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Review Article

Farid Forogh

Azerbaijan Medical University, Department of Cardiovascular Surgery, Baku, Azerbeijan

Effect of modified ultrafiltration in patients undergoing coronary surgery using cardiopulmonary bypass. A literature review

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Corresponding Author: Farid Forogh
Azerbaijan Medical University, Department of Cardiovascular Surgery, Baku, Azerbeijan
Email: farid.frogh@gmail.com

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Abstract

Aim: The purpose of this research is to describe the benefits of modified ultrafiltration (MUF) in cardiac surgery patients, especially in coronary revascularization patients.
Introduction: The modified ultrafiltration is the new generation of ultrafiltration, which is used to filtrates the excess water and low molecular weight substances like IL-6, IL-8, TNF and endothelin out of the blood. These excess fluid and low molecular weight substances are the main factors of post-operative complications in coronary artery bypass graft patients. There is limited information about the use of MUF in adult surgery, but is mostly used in congenital cardiac surgery patients. It is found to be very beneficial in pediatric cardiac surgery, but we need more data for using it in adult cardiac surgery
Material and Methods: This is a review article; in which we used the articles collected from world's creditable journals and platforms. These articles have published since 2000.
Results: From articles which we reviewed, 17 were about the benefits of MUF in congenital cardiac surgery and 8 articles were about the favorable effects of MUF in adult cardiac surgery. The rest of the articles were related indirectly to the MUF. About 5 of these researches proved the beneficial role of MUF on lungs functions after surgery, in 4 researches confirmed the significant decrease in post-operative bleeding and the need for blood transfusion, in 5 researches it has been measured that the level of inflammatory factors like interleukins, TNF and endothelin were decreased. In 6 articles the role of MUF in welfare of kidney functions were emphasized. And 1 article discussed about the benefits of MUF on cerebral metabolism correction. Nearly in all of the articles it was mentioned that MUF decreases the time of ventilation and vigorous urination after surgery.
Conclusion: Modified ultrafiltration (MUF) is a technique which decreases the post-operation complications due to cardio-pulmonary bypass, and could be beneficial in CABG patients.
Keywords: Modified ultrafiltration, coronary revascularisation, coronary surgery

INTRODUCTION

Ultrafiltration is the elder version of modified ultrafiltration, and it is a technique that can filtrate the fluid and low molecular weight substances out of a solution. This is not a new technology and the first paper entitled about "Osmotic Force" by Thomas Graham in 1854. After a long time, in 1924 for the first time the ultrafiltration used for clinical hemodialysis in patient who had uremic coma by George Haas, but unfortunately the patient didn't survive. Then in 1950s hemodialysis (has the same membrane and pressure mechanism for filtration) were used for treatment of uremia (1). Thomas Graham in his book he discussed about the separation of water out of a solution by the usage of a semipermeable membrane (2). Firstly, it was using for experimental purposes (separation of colloid and crystalloid substances from each other) and then it used in industries to produce pure fluid.

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For the performing of ultrafiltration, we need devices to filter the solution. The device principle is very simple. It has a chamber, semi preamble membrane and pressure applying system. The chamber is mostly a cylinder which enclosed by a semi-permeable membrane. The pressure applying system can be activated intermittently or continuously. The semi-preamble membrane is a micro-porous membrane, which allows just the fluid (mostly water) and low molecular weight substances to pass through and prevent the high molecular weight substances.

Mostly the process of separation of low molecular weight substances (from 10^3 to 10^6 Dalton) from solutions is used in chemical industries, especially for purifying protein solutions3. For ultrafiltration of macromolecules and cellular components of blood, membrane filters of 0.002–0.5 μm pore size are available. The pore size which is enough to filter viruses is from 0.03 μm to 1 μm, and for filtration of bacteria it should be from 0.5 μm up to 20 μm. Size cutoffs for membrane pores are usually expressed in terms of micrometers, while ultrafiltration cutoff is often expressed in terms of molecular mass (3).

Modified ultrafiltration (MUF) is a modified version of conventional ultrafiltration (CUF). MUF is a technique that can filtrate the fluid and low molecular weight substances out of the blood. The only difference of MUF from the CUF is in its time of the use. MUF is used at the end of CPB when the blood temperature is 38.5-39.5℃. But CUF is used before the end of CPB and during hypothermia.

The indication of MUF for the coronary artery bypass graft (CABG) patients is that they cannot tolerate the ischemia that comes due to hemodelution, so the MUF re-corrects this problem and filtrates excessive fluid out of blood. Besides the inflammatory system causes generalized inflammation activation due to blood touch to non-endothelial surface of oxygenator. This process is mediated by inflammatory mediators like cytokines (interleukins), TNF and endothelin. The MUF is claimed and proved that it reduces the level of these mediators in the blood and subsides the inflammatory process in CABG patients.

The researches show that the MUF is beneficial in all other kinds of cardiac surgery and its routine usage has decreased post-operative morbidity and hospital stay. So it is suggested that MUF routinely can be used.

Our experiences show that the decreasing in complications, decreasing of hospital stay and reanimation stay are decreasing the expenses on each patient and as a whole in coronary artery surgery. On the other hand the price of MUF device is no so high. So we can conclude that the use of MUF is very effective and efficient in cardiac surgery.

The fluid and low molecular weight substances which pass through the semi permeable membrane are called filtrate and rest of them are called retentate. The amount of the filtrates depended to the trans-membrane pressure, viscosity of fluid and total system resistance. This flow can be calculated with the following formula:

Calculation of flux in MUF: $J = \frac{TMP}{\mu Rt}$

In this formula, J is the filtrate flow, TMP is trans membranous pressure, μ is the viscosity of fluid and Rt. is the total resistance (4).

Ultrafiltration has been used in laboratories, purifying water, medical uses and so on. Astronauts use this technology for recycling and reuse of their own urine (5).

The management of complications after heart surgery with CPB are of important for heart surgeons. If this intervention is effective, it would be welcomed and appreciated. There are multiple post-operative complications which are related to the blood contact with oxygenator membrane surface of extracorporeal circulation and water retention to the body (6). The oxygenator surface which comes to contact with the blood and its components is causing reaction as a part of humeral immune system and the levels of IL-6, IL-8, endothelin and TNF are increased (7–9).

Meanwhile, cardiopulmonary bypass machines cause RBC and platelet destruction (10). The free hemoglobin and myoglobin precipitate in glomerular surface of kidneys and cause acute renal failure (11). This complication of the kidney can be avoided by prevention of prolonged aortic cross-clamping, intravascular hemolysis or contrast dye exposure (12). For the kidney injury creatinine is a creditable test to predict it (13). The inflammatory substances mostly cause activation of systemic inflammatory response syndrome (SIRS) and mostly increases the morbidity and mortality rate in open heart surgery patients. Coronary artery bypass graft (CABG) in patients who have already faced myocardial injury due to ischemia, is of serious risk for having infarction and decreasing the ejection fraction. Logically the inflammatory mediators and low level of oxygen due to hemodilution causes elevated amount of toxins and ischemia.

The hemodilution is caused by mixing the excessive fluid which is already exist into the CPB machine lines and this fluid is called priming fluid. The increase in the permeability of vessels causes leak of fluid into interstitial tissue, from which the pulmonary and cerebral edema are of consideration. ARDS is one of the most dangerous complications which can cause death. Although the patient is already in critical condition due to pulmonary edema which disturbs gas exchange in alveols (14). When the patient faces this critical condition, even by participation and interfere of multiple disciplines, the chance of death is very high (15). Brain edema is another challenging impact of fluid accumulation in body due to CPB. Using of MUF decreases the edema of brain and improves the metabolic recovery of it (16). During the heart operation under cardiopulmonary bypass relatively huge amount of fluid enters into the blood circulation. This excessive water causes hemodilution and decreases hemoglobin and hematocrit level significantly. So the tissue oxygen supply in the body is impaired and decreases, and in turn intensifies the heart ischemia and can be detected by post-operative measurement of Troponin-I in the blood. Not only this but also hemodilution causes coagulation cascade dysfunction, which is in turn causes

post-operative bleeding and increase for post-operation needs for blood transfusion (10). Whole of these complications causes an increase in the consumption of banked blood by the tertiary hospitals. Some researches confirm this issue and indicate that the heart surgery is the biggest consumer of banked blood (especially packed red cells) in developed countries. In these reports it has been found that the chance of suture line bleeding in CABG operation has causative relationship with hemodilution and was found to be the main cause of reoperation (17).

By the mentioned articles it has been found that a significant decrease in the hemoglobin (less than 6 gram/dl) and hematocrit (less than 17 g) are not match the minimal level of needs to perfuse the heart post-operatively and must be in consider peri-operatively (18). This scenario is getting worst by the combination of pulmonary edema to the hemodilution due to the fluid retention, which can make a barrier in front of alveolar gas exchange.

Beside of fluid retention in systems, the activation of inflammatory system has a major rule in post-operative complications after heart surgery (8). For the prevention and treatment of these complications several interventions are available. These interventions are anti-inflammatory drug therapy and the use of modified ultrafiltration, which are done after discontinuation of CPB.

The technic of modified ultrafiltration (MUF) is used for filtration of excessive fluids which entered in the patient circulation and low molecular weight compounds (inflammatory mediators like IL-6, IL-8…) out of blood. By this mechanisms MUF decreases the morbidity and mortality of heart surgery patients and also decreases the chance of development of systemic inflammatory response syndrome (SIRS) (19,20). But some authors are not agree that the MUF decreases the adhesion molecules and TNF. Even in a research by Torina et-al it has been found that the MUF decreases the chance of post-operative bleeding, but it increases the level of adhesion molecules and TNF (21). MUF can be used either Arteriovenous (AVMUF) or veno-arterial (VAMUF). The AVMUF is very common method of MUF but VAMUF seems to be more physiologic 21. The amount of fluid that can be taken out by MUF is respectively depended to some parameters like priming fluid in the CPB lines, blood transfusion during operation, patient's diuresis during operation, calculation of invisible fluid loss, NG-tube secretions and vital signs (22,23).

The diluted blood with excess fluid is not physiologic and sufficient for ischemic heart and the MUF decreases the volume by bringing out the excess fluid out of the circulation and causes hemo-concentration. On the other hand it decreases the vigorous urination which is not physiologic (24). The hemo-concentration of the blood has the benefit of the normalization of coagulation system and hematocrit level in the blood (25–28). There are some researches show that the use of MUF by the mentioned mechanism of normalizing the coagulation system, prevents post-operative bleeding (29) and the needs for blood transfusion post-operatively (30–36). The effectiveness of MUF is studied well in pediatric heart surgery (37), but still it is new in adult cardiac surgery and many questions are remain unanswered in this field (38).

RESEARCH AND DESIGN METHODS

Research Design

The MUF is used in a lot of centers after CPB of congenital heart surgery, but there is limited hospitals in which they use MUF for adults. That is because this technology is newly used in heart surgery era, so there is less information about it in adult heart surgery. On the other hand it was started to be used in children first; because the fluid retention is more sever in children and their kidneys can't filtrate all excess fluid out of circulation.

This is a review article research, which is an observational research on research papers which have been published since year 2000.

Research Paper Selection

To fine and select materials and research articles about our selected topic, we used PubMed, Google Scholars, COCHRANE, SCOPUS and WHO Hinari, with keywords of modified ultrafiltration, MUF, CABG, CPB complications and heart surgery complications.

The exclusion criteria was the retracted articles, the articles from noncreditable journals, and articles from predatory journals.

Methods

This is a review article about the usage of modified ultrafiltration (MUF) during surgical coronary revascularization. For this reason, we searched in some credible internet platforms like PubMed, Google Scholars, COCHRANE, SCOPUS and WHO Hinari to find articles directly or indirectly related to modified ultrafiltration (MUF) and coronary artery bypass grafting (CABG). Then we studied critically these articles one by one without any pre-judgement and then collected all the findings from them.

The inclusion criteria for choosing the articles was some characteristics like being related to the topic, being published in creditable journals, not been retracted, no conflict of interest and published after year 2000.

The exclusion criteria were research articles from predatory journals and retracted articles.

RESULT

From the articles which we reviewed, 18 articles were about the benefits of MUF in congenital heart surgery and 8 articles were about the favorable effects of MUF in adults cardiac surgery. But in the mentioned 8 articles the CABG patients were consist with other diseases. About 5 of these researches proved the beneficial role of MUF on lungs functions after surgery, in 4 researches confirmed the significant decrease in post-operative bleeding

and the need for blood transfusion, in 5 researches it has been measured that the level of inflammatory factors like interleukins, TNF and endothelin were decreased. In 6 articles the role of MUF in welfare of kidney functions were emphasized. Nearly in all of the articles it was mentioned that MUF decrease the time of ventilation and vigorous urination after surgery (Table 1) (Figure 1).

Table 1. The number of articles

Articles	Numbers
Congenital	18
Adult	8
Efficacy of MUF on lungs	5
Decrease in post-operative bleeding	4
Decrease in inflammatory factors	5
Normalization of kidneys function	6
Cerebral metabolism correction	1

Ju¨rg Gru¨nenfelder et al. found that the level of cytokines (interleukins, TNF and endothelin) increases during CPB. MUF decreases the abnormal level of these cytokines significantly (22). Also according to the Preeshagul, Halter, Poli and their coleaques, the oxygenator surface which come to contact with the blood and its components is causing reaction as a part of humoral immune system and the levels of IL-6, IL-8, endothelin and TNF increased (7–9) (Table 2).

In 5 articles (articles 11, 12, 13, 20, 24 and 33) the role of MUF in welfare of kidney functions were emphasized. The free hemoglobin and myoglobin precipitate in glomerular surface of kidneys and causes acute renal failure (11). This complication of the kidney can be avoided by prevention of prolonged aortic cross-clamping, intravascular hemolysis or contrast dye exposure (12). For the kidney injury creatinine is a creditable test to predict it (13).

CPB causes lungs edema and difficulty in front of blood oxygenation (14). MUF decreases the chance of pulmonary edema and filters the harmful inflammatory mediators and these mechanisms can protect the lungs during the cardiac surgery (15,29), and increases blood arterial gas level (36).

MUF buildups the level of platelets and coagulation factors and by this mechanism prevents from suture line, sternum and LIMA bed bleeding post-operatively (27,31,32), on the other hand when there is low bleeding, there is low chance of need for blood transfusion (18,36,39).

In 1 article it has been proved that the MUF decreases the incidence of brain edema (16). Nearly in all of the articles it was mentioned that MUF decrease the time of ventilation, vigorous urination after surgery, ICU stay and finally hospital stay respectively.

DISCUSSION

The modified ultrafiltration normalizes the level of the hemoglobin and hematocrit by removing the excess amount of water out of blood circulation. By this mechanism it nearly normalizes the

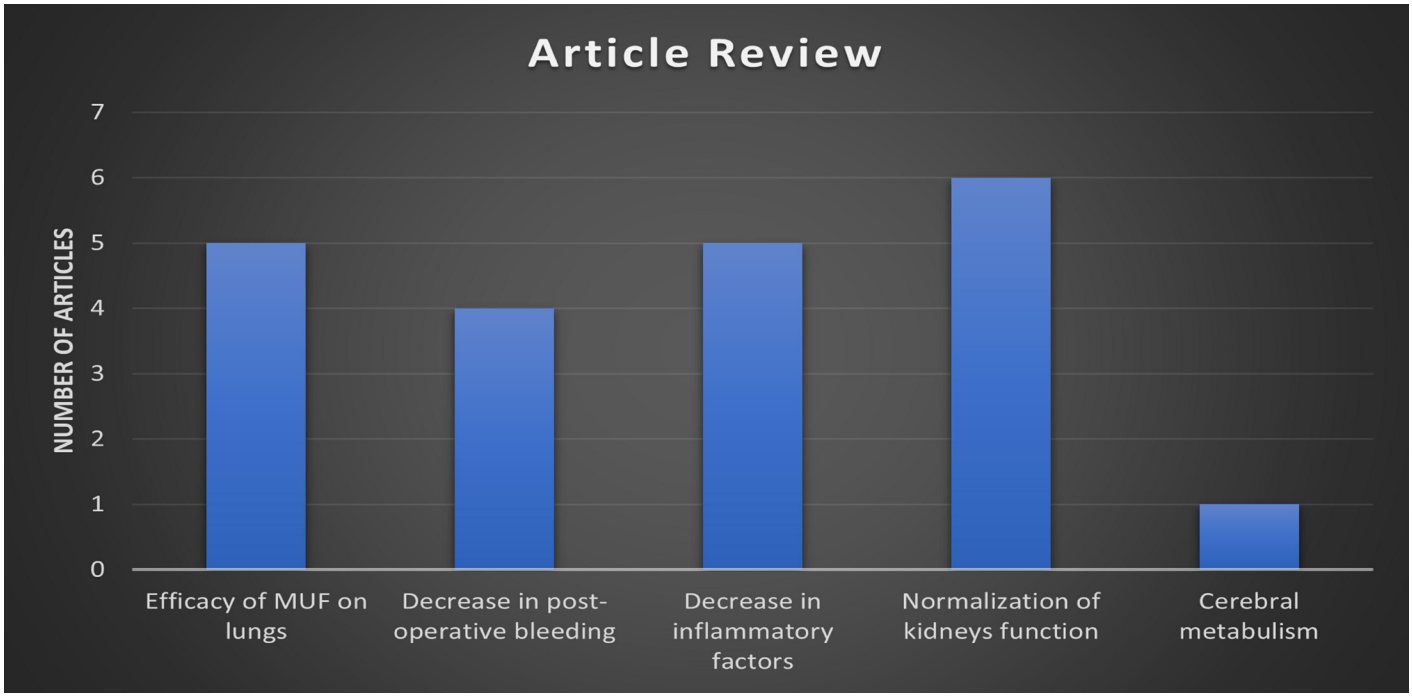

Figure 1. The numbers of the articles and the areas they discussed

Table 2. The number of patients in different articles and their findings

Study of system	Article name	Method	Number of participants	Patients	Control	Finding
welfare of kidney functions with MUF	Kandil OA, Motawea KR, Darling E, et al.	meta-analysis	8005	2165	5840	Ultrafiltration and cardiopulmonary bypass associated acute kidney injury
	Mohammed H, Raslan A, Rahman AAA, Mahmoud HF	RCT	40	20	20	Impact of modified ultrafiltration on Cardiac Surgery-Associated Acute Kidney Injury.
	Karadem KB, Abud B, Kunt AG.	RCT	113	113	226	The Effect of the Hemofiltration-Body Surface Area on the Mortality and Morbidity during Cardiopulmonary Bypass. Published online
	Zahoor M, Abbass S, Khan AA, Ahmad SA.	RCT	50	50	100	MODIFIED ULTRAFILTRATION : ROLE IN ADULT CARDIAC SURGICAL HAEMOSTASIS.
	Arwel O. et al.	RCT	21	21	42	Effects of Modified Ultrafiltration on Arterial Blood Gas After Cardiopulmonary Bypass in Children.
	Low ZK. Et al.	meta-analysis	610	626	1236	Modified ultrafiltration reduces postoperative blood loss and transfusions in adult cardiac surgery
MUF buildups the level of platelets and coagulation factors and prevent post of blood lose	Hu J, Li P, Chen X, Yan J, Zhang J, Zhang C.	Meta-analysis	202	203	405	Effects of modified ultrafiltration and conventional ultrafiltration combination on perioperative clinical outcomes in pediatric cardiac surgery.
	Badkal A, Baviskar A, Thakre A.	Observational study	30	30	60	Observational Study for the Effect of Modified Ultra filtration in Adult Cardiac Surgery
	Bechtel JFM, Sievers HH, Leyh RG, Bartels C, Joubert-hu E	RCT	15	15	30	effects of modified ultrafiltration on coagulation
	Elmistekawy EM, Errett L, Fawzy HF. center:	A prospective observational study	52	53	105	Predictors of packed red cell transfusion after isolated primary coronary artery bypass grafting - The experience of a single cardiac
MUF decreases the incidence of brain edema	Skaryak LA, Kirshbom PM, Kern FH, Greeley WJ	RCT	14	14	28	Ungerleider RM, Gaynor JW. MODIFIED IMPROVES CEREBRAL METABOLIC RECOVERY AFTER CIRCULATORY Venous line rterial line Ultrafilter Outlet of UF connected to filtrate port Roller pump at inlet of

oxygenation of the end organs like kidneys, liver, gastrointestinal system, brain, and myocardium. Myocardium is already in ischemia, so hemodilution due to entering of excess fluid, like priming fluid in CPB lines, blood transfusion, crystalloid and colloid serum infusion, drug infusion and sleeting water during tying knots, cause decrease in oxygen supplying to the vital end organs. On the other hand, this low level of oxygenation, causes sympathetic discharges and tachycardia. This tachycardia increases the myocardial needs for oxygenation and is making a defective cycle which mostly ends to disasters like arrhythmias and failure. MUF cuts this chain by normalizing the hemoglobin and hematocrit concentrations.

Activation of the inflammatory substances like cytokines, TNF and endothelin are the triggers of inflammatory system activation in the body during and after on-pump heart surgery. The blood come to the contact with the non-endothelium surface and this contact causes activation of both cellular and humeral defense system. Jeffrey Halter and colleagues declared that Cardiopulmonary bypass causes a systemic inflammatory response syndrome or SIRS, which can be ended to acute lung inflammation known as post-perfusion syndrome. They believe that SIRS, causes by elevation of cytokines after CPB, and causes post-operative pulmonary dysfunction and they called it Phase I, and in the second phase, the interleukin-6 (IL-6)

is predominantly released from the heart in CPB patients (8).

Poli et al were discussed about the effects of cytokine clearance on the decreasing the chance of post-operative complication in cardiac surgery patients (9). As we know cytokines in CABG patients can destroy the pulmonary cells and their clearance can help to decrease the chance of SIRS and it can only be prevented by cytokines clearance with the MUF (19,22). So we can conclude that it will be very beneficial for CABG patients to keep blood saturation high.

Besides of the inflammatory mediators, the identification of biomarkers that provide evidence supporting clinical outcome has greatly supportive, helping clinicians in many medicine sub-specialties to forecast clinical course. Isabel Preeshagul et al, have discovered that biomarkers like Troponin-I may be used as patient's status. In this review, they assessed cardiac biomarkers as predictors of clinical outcome for post-operative CABG patients.

There are some studies that show no significant decrease in ventilation time with using the MUF after CPB (maybe due to 12-24 hours' ventilation protocol which is mandatory in some centers). Zhao Kai Low et al, in a meta-analysis on 726 patients found that there was no significant difference detected (mean difference -0.47 h, 95% CI -2.05 to 1.12 h, P = 0.56) in ventilation duration post-operatively after using MUF in cardiac surgery patients (39).

Decreasing the post-operative bleeding and blood transfusion are a very convincing reason to use MUF post-operatively. Because it is said that it buildup the level of platelets and coagulation factors and by this mechanism prevents from suture line and LIMA bed bleeding post-operatively (27,31,32), on the other hand when there is low bleeding, there is low chance of need for blood transfusion (18,36,39). With doing this, it also prevents the body from harmful effects of blood transfusion.

The most intolerance to the ischemia after brain is known to be kidneys. MUF showed that the use of it caused saving the kidneys relatively from the side effects of CPB. Omneya A. Kandil and colleagues found that the harmful effects of CPB can be prevented by ultrafiltration of blood and it is useful even in chronic ischemic injured kidney (11). The CPB puts the kidneys to ischemic state and on the other hand inflammatory substances and free hemoglobin harms the nephrons (12,13,20,24).

The lungs function during the CPB will be frustrated. Because from one side interstitial pulmonary edema creates a barrier in front of gas exchange and on the other hand the some mediators causes SIRS (as we discussed before) (14). MUF decreases the chance of pulmonary edema and filters the harmful inflammatory mediators and these mechanisms can protect the lungs during the cardiac surgery (15,29), and increases blood arterial gas level (36). One study shows that the normal oxygenation will also protect brain by normalizing the cerebral metabolisms (16).

With all these benefits, the effects of MUF on morbidity and mortality is under observation and some studies like the works of Joel Bierer and his colleagues show that MUF decrease recovery duration and morbidity and mortality as well (38).

CONCLUSION

We found that the modified ultrafiltration (MUF) is a technique which decreases the post-operation complications due to cardio-pulmonary bypass in cardiac surgery, and is effective in CABG patients. The most significant findings were the decrease in the number of post-operative bleeding and blood transfusion need, decrease in the level of interleukins, TNF and endothelin, decrease in pulmonary edema, causes lungs and kidneys protection.

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